The Synthesis of Unsaturated Amino-Ethers and the Reduction of Imines with Lithium Aluminum Hydride

By

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PREFACE

The material in this dissertation is presented in detailed form to facilitate duplication by future investigators. Although the procedures employed for the preparation of members of a homologous series are quite similar in many cases, the method of preparation of each new compound is given separately.

All temperatures refer to the centigrade scale, and its symbol is omitted.

The boiling points and melting points are all corrected values. The thermometers used were calibrated against a set of thermometers standardized by the Bureau of Standards. Boiling points represent boiling temperature at atmospheric pressure unless otherwise indicated.

Pressures above 10 mm. were read with a Zimmerli gauge calibrated against a Stokes-McLeod gauge. Pressures below 10 mm. were read with a Stokes-McLeod gauge.

The atomic refractions used throughout this research in calculating theoretical values of molar refractions were those published by Vogel, J. Chem. Soc. 1948, 1942. They were compiled by him from various publications and experiments of the previous five to fifteen years.

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CHAPTER I

INTRODUCTION AND REVIEW OF THE LITERATURE

The Office of Naval Research sponsored a portion of the research described in this dissertation. It was specified that the compounds prepared should be liquids containing one or more amino groups and one or more unsaturated linkages. Certain other functional groups, including the ether and the alcohol, were also permissible. It was decided that the phase of the project represented by this dissertation would be concerned primarily with the synthesis of unsaturated amino ethers. Amino alcohols which were an integral part of the project were also prepared and employed in the syntheses of their corresponding allyl ethers.

Included in this dissertation is a new method for the synthesis of secondary alkylamines. It consists of the reduction of aldimines with lithium aluminum hydride. It has been shown that unsaturated amines can also be prepared by this method.

Chapter II has been included to discuss various unsuccessful attempts. It is hoped that the inclusion of this chapter will save future investigators in this field some time and effort. Some conclusions which have been drawn from these attempts are given in Chapter V.

The alkene oxides are a particularly interesting type of ether. The size of the ring produces strain in the bonds linking its members and causes the compounds to be very active. Their reactivity gives them extensive usefulness in organic syntheses.

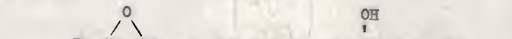
One of the two general methods which have been employed to prepare alkene oxides is the dehydrohalogenation with alkalies of compounds containing the structure below, where X is a chlorine or bromine atom:

1,2-Epoxy-3-chloropropane (commonly called epichlorohydrin) was first synthesized by Reboul in 1861 by this method.[1] Others who have employed the method are Müder and Tollens in 1871[2], Prevost in 1875[3], Claus in 1877[4], Fairbourne, Gibson, and Stephens in 1930[5], Griesheim in 1910[6], and Braun in 1932[7]. The alkalies employed were sodium, potassium and calcium hydroxides.

The other method employed in the synthesis of alkene oxides is the oxidation of olefins. In recent years these oxides, especially ethylene oxide and epichlorohydrin, have become available in large scale commercial quantities through discovery and development of processes using direct catalytic air-oxidation of the corresponding olefins. On the laboratory

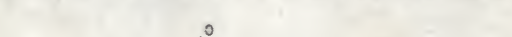
scale, the alkene oxides may be prepared by oxidation of olefins with perbenzoic acid as was first done by Prileschajew in 1910[8,9].

Alcohols, amines, ammonia, water, and acids--all containing an active hydrogen atom--react with the alkene oxides:



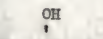
R'--H represents any compound having a labile hydrogen atom. With ethylene oxide, this method may be employed to introduce the hydroxyethyl group ($-C_2H_4OH$) into many types of compounds. A product which contains the hydroxyethyl group is more soluble in water and boils at temperatures from 50 to 200° higher than its parent compound[10].

This reaction, which provides a convenient method for introducing a primary alcohol group, is a stepping stone to other derivatives. It was for this purpose that ethylene oxide was employed in this investigation. For example, with a secondary amine the equation for the reaction may be written:

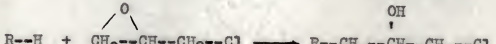


In epichlorohydrin, both the epoxy group and the

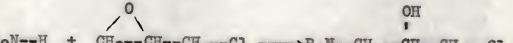
chlorine atom are highly reactive. In most of its reactions, however, the compound behaves primarily as an epoxide, initially combining through the epoxy group with substances containing an active hydrogen atom to form compounds of the type:



An equation for the reaction may be written as:

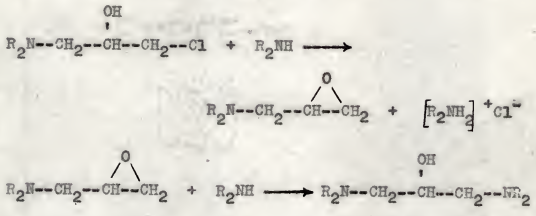


R--H represents any compound having a labile hydrogen atom. The initial reaction with the epoxide group occurs even with such compounds as nitrogen bases which normally effect direct replacement of an active organic halogen atom through metathesis:

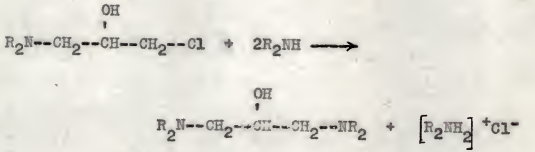


With an excess of the amine the reaction may proceed a step farther. There are two mechanisms by which it may occur:

(1) Through the formation of the epoxide, the amine acting as a base:

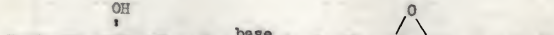


(2) By direct metathesis:

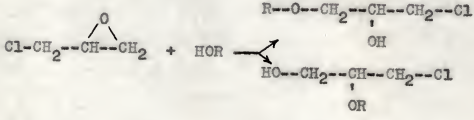


Which mechanism predominates in any given case depends upon the relative speeds of the competing reactions and the basicity of the amine employed. The stronger the base, the more likely is the formation of the epoxide. It is probable that in most cases the reaction proceeds through both mechanisms. The action of an alcohol on epichlorohydrin proceeds by its addition at the epoxide group in a manner that forms the 1-chloro-2-hydroxy-3-alkoxypropane derivative:

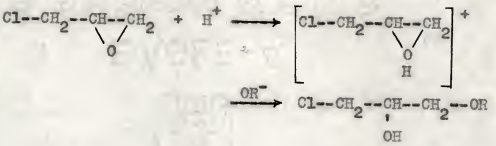
The lower primary and secondary alcohols combine with epichlorohydrin at moderate temperatures in the presence of acidic catalysts such as sulfuric[11-14] and hydrofluoric acids[15], boron trifluoride[16], and stannic chloride[17] and other metal halides[18]. The greater the molecular weight, the higher is the reaction temperature necessary to accomplish the synthesis. The product of the alcohol-epichlorohydrin reaction may be converted with a base to the epoxide which in turn may be reacted again with more of the alcohol.



It might at first appear that the reaction of an alcohol with epichlorohydrin would produce the primary and the secondary alcohols:

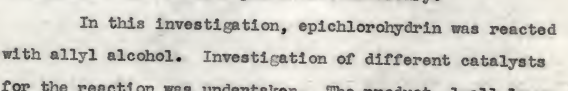


Many examples of secondary alcohol formation may be found in the literature, but it was left to D. Swern, G. N. Billen, and H. B. Knight to prove that no primary alcohol was formed. They also proposed an electronic interpretation when the reaction proceeds in the presence of an acid catalyst[19]:



T. K. Todson, C. B. Pollard, and E. G. Rietz have shown that mercaptans also form the secondary product[20]. The fact of secondary alcohol formation has been so well established that further proof is unnecessary.

In this investigation, epichlorohydrin was reacted with allyl alcohol. Investigation of different catalysts for the reaction was undertaken. The product, 1-allyloxy-2-hydroxy-3-chloropropane was reacted directly with secondary amines without having been converted to the epoxide.



$$CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_2{-}Cl \;+\; 2HNR_2 \longrightarrow$$

$$CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_2{-}NR_2 \;+\; \left[R_2NH_2\right]^{+}Cl^{-}$$

The results supported the work of C. B. Pollard and T. H. Wicker (Unpublished) of these laboratories.

Also, 1,3-bis-dialkylamino-2-hydroxypropanes were prepared by reaction epichlorohydrin with an excess of secondary amines.

$$H_2C\underset{\diagdown\,\diagup}{O}CH{-}CH_2{-}Cl \;+\; 2HNR_2 \longrightarrow$$

$$R_2N{-}CH_2{-}\underset{\displaystyle OH}{\underset{|}{C}}H{-}CH_2{-}NR_2 \cdot HCl$$

The amino alcohols and ether amino alcohols thus prepared were converted to their respective allyl ethers by the Williamson synthesis. Sodium and potassium were used to prepare the sodium and potassium alkoxides. Since potassium is more electro-positive, it might be expected that with high molecular-weight alcohols it would be more effective. This proved correct.

Several difficulties were encountered; they were overcome by varying the procedure. It is probable that some

of the procedures given in Chapter III, Procedures for Syntheses of Unsaturated Amino-Ethers could have been improved upon. For this reason the recommended general procedures for various reactions are given in Chapter V, Conclusions and Discussion of Experimental Results.

The second phase of the research described in this dissertation deals with the synthesis of aliphatic imines and the reduction with lithium aluminum hydride of aliphatic imines to produce secondary amines.

Unsymmetrical secondary aliphatic amines are sometimes difficult to prepare. Probably the method most used has been the reaction of an alkyl halide and a primary amine. Replacement of halogen atoms by substituted amino groups, which may be termed aminolysis[21], is usually feasible and is employed extensively in the synthesis of amines[a]. This

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[a]For example, 2-dipropylaminoethanol could have been prepared for this investigation from ethylene chlorohydrin and dipropylamine:

$$2(C_3H_7)_2NH + Cl{-}CH_2{-}CH_2{-}OH \longrightarrow (C_3H_7)_2N{-}CH_2{-}CH_2{-}OH + \left[(C_3H_7)_2NH_2\right]^+Cl^-$$

Instead it was prepared from the amine and ethylene oxide. However, other secondary amines were prepared by direct metathetical replacement of an active organic halogen atom by a nitrogen base.

$$2RNH_2 + R'Cl \longrightarrow R{-}\overset{H}{N}{-}R' + \left[RNH_3\right]^+Cl^-$$

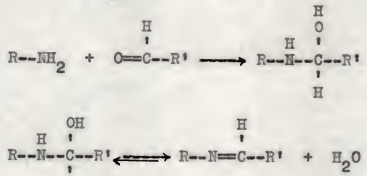
method is simple, but it does have disadvantages such as the necessity of an excess of amine to remove the hydrogen halide and to minimize the amount of tertiary and quaternary salt formed as by-products. Sodium bicarbonate may be employed to combine with the hydrogen halide, but an excess of amine would still be advantageous to minimize by-product formation. Another difficulty is that starting materials are not always at hand; therefore, alternative methods are always welcome.

That carbonyl compounds can be hydrogenated in the presence of ammonia to produce mixtures of primary, secondary, and tertiary amines is a well-known fact. Both nickel[22] and Raney nickel[23,24], with hydrogen under pressure of 20 to 150 atmospheres and temperatures up to 150°, have been employed as catalysts. A low-pressure, reductive alkylation for the conversion of ketones to primary amines has been reported by E. R. Alexander and A. L. Misegades. The reaction was carried out in the presence of an excess of ammonium chloride. The medium used was methanol saturated with ammonia, and the catalyst was platinum oxide[25]. Maintaining reaction conditions which would produce the desired primary amine with the minimum amount of the secondary base was difficult in many cases.

R. C. Fuson has stated the addition of ammonia to ketones probably occurs but, if so, the addition compounds

are too unstable to be isolated[26]. This statement has been supported by this investigation. There are many ketone reactions, however, which have been explained by assuming the formation of adducts of ketones and ammonia. The Leuckart reaction[27], for instance, is the conversion of a ketone to the corresponding amine by heating with ammonium formate. 2-Isopropylaminoethanol can be prepared at low pressure from acetone and ethanolamine[28].

The normal reaction between an aldehyde and a primary amine results in the formation of water from the oxygen of the carbonyl group and the hydrogen of the amine to yield an aldimine. The products are often called Schiff bases. The mechanism probably involves the formation of the carbonyl-amine addition intermediate[29]:



Louis and Henry reported the reaction in 1893[30,31]. Tiolais has done an extensive amount of investigation in this field, including the synthesis of many of the aliphatic aldimines[29]. Several other workers have reported the preparation of various aliphatic aldimines[30-34].

Most of the investigators have attempted the reduction of these imines. Campbell, Sommers, and Campbell used absolute ethyl alcohol as the solvent, palladium-charcoal catalyst, and hydrogen under two or three atmospheres pressure[30]. Skita and his co-workers investigated low-pressure catalytic hydrogenation, using platinum as catalyst and acetic acid as solvent[35,36]. Winans and Adkins[37] and Henze and Humphreys[38] have shown that aldehyde-amine condensation products can be hydrogenated to secondary amines at high pressures in the presence of nickel catalysts. Reduction of aliphatic aldimines by sodium and alcohol has also been reported[39,33,34]. These various methods produce secondary amines in most cases, but each method has serious practical faults. The sodium-alcohol reduction does not always give good yields. The nickel catalyst-high-pressure method does give good yields, but it involves the use of high-pressure hydrogenation equipment. The use of platinum or palladium-charcoal is costly, and the latter is not easy to prepare.

Nystrom and Brown reduced benzalaniline to N-benzylaniline (93 per cent yield) with lithium aluminum hydride[40]. Report of the reduction of no other imine with lithium aluminum hydride has been found in the literature. Since there was a need for a simple method of reduction of aliphatic imines, the author investigated the feasibility of employing

the procedure of Nystrom and Brown. A modification of their method has been developed in this research for the reduction of aliphatic aldimines.

Lithium aluminum hydride is one of the most versatile reagents discovered since the Grignard reagent to which it is in many ways quite similar. It was first prepared by Finholt, Bond, and Schlesinger in 1947[41]. Some preliminary experiments were carried out by Finholt, Schlesinger and Wilzbach to ascertain its behavior toward several common types of organic compounds. These experiments indicated that this hydride will reduce carbonyl, carbalkoxy, acyl-chloride and nitro groups, but will not act on the double bond of simple olefins. Nystrom and Brown investigated these properties more fully[40, 42]. They have pointed out many advantages of lithium aluminum hydride:

> The attractive features of lithium aluminum hydride as a reagent which, combined, place it in a unique position are (1) that it is easily prepared on either a large or small scale from commercially available lithium hydride, (2) that it is indefinitely stable at room temperature, (3) that it is ether-soluble, (4) that as compared with other reducing agents, excepting hydrogen, it has a favorable ratio of reducing capacity to mass, (5) that the reductions occur at room temperature, and (6) that no unusual equipment is needed.

The equations, as given by Nystrom and Brown, for the reduction of various types of compounds with lithium aluminum hydride are reproduced below:

Aldehydes and ketones:

$$4R_2CO + LiAlH_4 \longrightarrow LiAl(OCHR_2)_4$$

Esters:

$$2RCOOR' + LiAlH_4 \longrightarrow LiAl(OR')_2(OCH_2R)_2$$

Acid chlorides:

$$2RCOCl + LiAlH_4 \longrightarrow LiAlCl(OCH_2R)_2$$

Acid anhydrides:

$$(RCO)_2O + LiAlH_4 \longrightarrow LiAlO(OCH_2R)_2$$

Alkyl halides:

$$4RX + LiAlH_4 \longrightarrow 4RH + LiAlX_4$$

Nitriles:

$$2RCN + LiAlH_4 \longrightarrow (RCH_2N)_2LiAl$$

Aromatic nitro compounds:

$$RNO_2 + LiAlH_4 \longrightarrow \tfrac{1}{2}R{-}{-}N{=}{=}N{-}R + LiAlO_2 + 2H_2$$

Aliphatic nitro compounds:

$$2RNO_2 + LiAlH_4 \longrightarrow (RN)_2LiAl + 2LiAlO_2 + 6H_2$$

Azoxy compounds:

$$2RN_2OR + LiAlH_4 \longrightarrow 2R{-}{-}N{=}{=}N{-}{-}R + LiAlO_2 + 2H_2$$

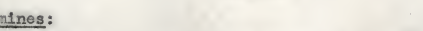
Epoxides:

$$4R(CHCH_2)O + LiAlH_4 \longrightarrow \left[RCH(CH_3)O\right]_4LiAl$$

Amides:

$$2RCONR_2 + LiAlH_4 \longrightarrow 2RCH_2NR_2 + LiAlO_2$$

Aldimines:



Nystrom and Brown found that reductions with lithium aluminum hydride take place with extreme rapidity and with virtually no side-reactions. The yield appears to be limited principally by the efficiency of the procedures employed in isolating the product. This has also proved to be true in the reduction of the alkyl aldimines reported in this investigation. The procedure of Nystrom and Brown has been modified, and the results of several reductions are given. The secondary amines were verified by their physical constants and derivatives.

CHAPTER II

REACTIONS WHICH DID NOT PRODUCE DESIRED PRODUCTS

Although the attempts discussed in this chapter were unsuccessful from the standpoint of producing new compounds, several significant observations have resulted from this experimental work. These are discussed in Chapter V, Conclusions and Discussion of Experimental Results. It is probable that study of this chapter would facilitate avoiding similar difficulties in future projects in this field. The discussion presented includes references to the literature and claims of other investigators of similar problems.

Alkyl-dialkylaminomethyl Ethers

Three different types of reactions were employed in an unsuccessful attempt to prepare these ethers. Each type of reaction is described in the following pages.

Mannich-type Condensation of Formaldehyde with an Alcohol and a Secondary Amine:

$$R\text{--}OH + HCH(=O) + HNR_2 \longrightarrow R\text{--}O\text{--}CH_2\text{--}NR_2 + H_2O$$

McLeod and Robinson have claimed that alkyl-dialkylaminomethyl ethers can be prepared by the condensation of formaldehyde, a secondary amine, and an alcohol[43]. The equation given for the reaction was proposed in their report.

Potassium carbonate was used as the dehydrating agent. Yields were reported to be greater when only one molecular portion of the alcohol was employed and when high molecular weight alcohols were used. It was claimed that diethylaminomethyl-isoamyl ether was obtained in a yield of 58 per cent of that demanded by theory.

Many of these compounds were reported to be hydrolyzed by water alone, and all of them were hydrolyzed very readily with dilute hydrochloric acid. The odors of all these substances were reported to be "in part characteristic and in part due to the products of hydrolysis". The only physical constants given by the above authors for their compounds were boiling points and neutralization equivalents. Carbon and hydrogen analyses were determined on only two

compounds.

The general procedure followed in an attempt to prepare ethyl-(N-allyl-n-butylaminomethyl) ether, allyl-(di-n-butylaminomethyl) ether, and allyl-(diisopropylaminomethyl) ether which is an adaptation of that reported by McLeod and Robinson was:

One mole of an aqueous solution of formaldehyde was added slowly to one mole of secondary amine, and a mole of the alcohol was then similarly added. The solution was saturated with anhydrous potassium carbonate. These reactants, maintained at ice-bath temperature throughout the reaction period, were stirred for an hour; then the non-aqueous layer was separated and dried overnight with anhydrous potassium carbonate. Fractionation in each case yielded the starting materials and high-boiling residues.

An attempt was made to repeat the work of McLeod and Robinson in preparing isobutyl-diethylaminomethyl ether. Their procedure was carefully followed twice, but upon fractionation a very wide boiling range existed (60-190°). As has been quoted, McLeod and Robinson stated that the odors of the compounds were in part due to the product of hydrolysis--that is, the starting materials. It is believed that if these authors did obtain any of the compounds, they did so by distilling very rapidly before hydrolysis could be complete. It was concluded that if following their procedure

produced the compounds they hydrolyzed back to the starting materials too easily to be of any value on this project.

Reaction of Chloromethyl-alkyl Ether and a Secondary Amine:

$$CH_3{-}O{-}CH_2{-}Cl + 2HN(CH_2{-}CH_2{-}CH_2{-}CH_3)_2 \longrightarrow CH_3{-}O{-}CH_2{-}N(CH_2{-}CH_2{-}CH_2{-}CH_3)_2 + \left[(CH_3{-}CH_2{-}CH_2{-}CH_2)_2NH_2\right]^+Cl^-$$

Chloromethyl-methyl ether was prepared by adaptation of the method developed by Henry[44] which was described by Marvel and Porter[45].

To 258.5 g. (2 moles) of di-n-butylamine in a one-liter, three-necked flask fitted with a stirrer, reflux condenser and dropping funnel were added 80.5 g. (one mole) of chloromethyl-methyl ether. The contents of the flask were chilled in an ice-bath during the one-half hour addition.

A reaction proceeded rapidly, and di-n-butylamine hydrochloride precipitated. After the mixture had been stirred an additional half-hour, 300 ml. of ether were added and the mixture was filtered. The precipitate was washed with ether and dried. An almost theoretical amount of amine hydrochloride was obtained.

The filtrate and washings were combined and distilled through a Vigreux column. Part of the ether was removed at atmospheric pressure, and the remainder was stripped at 10 mm. About 250 ml. of material was collected at 150-160°/10 mm. This fraction was redistilled three times, and the boiling range was narrowed to 155-157.5°/10 mm.

Physical constants of this fraction were:

Density (d^{25}_4).....	0.8060
Refractive Index ($n^{25}D$).....	1.4410
Molar Refraction (MR_D):	
Theoretical (for methyl-di-n-butylaminomethyl ether)	54.00
Found.....	56.64
Analysis -- Nitrogen, %:	
Calculated.....	8.09
Found.....	8.03

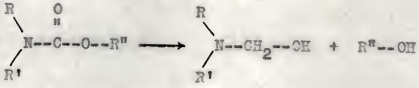
The theoretical neutralization equivalent for methyl-di-n-butylaminomethyl ether is 173.3; but that determined in 50 per cent isopropanol, using brom-cresol-green indicator, was 139.0.

These data indicate that the compound was hydrolyzed very rapidly if it ever formed. From the yield of di-n-butylamine hydrochloride obtained and from the great heat of reaction, it seems highly probable that the reaction did take place. The difficulties encountered in purification and the

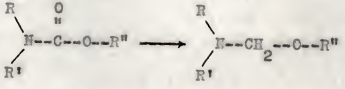
hydrolysis of product were similar to those which prevented the preparation of similar compounds following the procedure reported by McLeod and Robinson.

Attempted Reduction of Urethans:

(a) Reducing as an ester, by splitting the ester-linkage, to produce alcohols



(b) Reducing as an amide, to produce an amino-methyl ether



References to the reduction of urethans could not be found in the literature. Since a urethan is somewhat similar to both an amide and an ester, it might be expected that the reduction would proceed by one of the reactions proposed in the above equations. It was hoped that the second possibility would materialize.

Esters, by reduction with nascent hydrogen, split and produce two alcohols. To avoid this, reduction by hydrogen

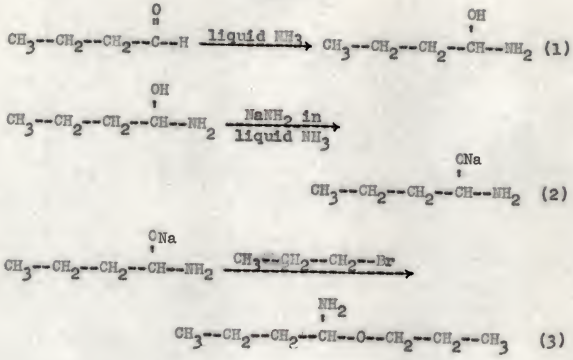
in a bomb-reactor was attempted.

Thirty-three and one-half grams of ethyl-n-butyl-carbamate in 70 ml. of absolute alcohol were placed in a stainless steel bomb with 5 g. of Raney nickel catalyst. The mixture in the bomb was subjected to hydrogen pressure of 1500 lbs./sq. in. at temperatures between 100 and 140° for ten hours in a rocking-arm autoclave. The ethyl-n-butyl-carbamate was recovered quantitatively, indicating no possibility of reduction.

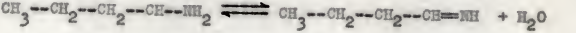
None of these three methods for the synthesis of mono- and di-alkylaminomethyl alkyl ethers showed much promise. It is probable that the desired products formed by the first two methods. However, all yields were extremely low, and little of the products remained. Both general instability and ready hydrolysis of aminomethyl alkyl ethers contribute to this result.

Investigation of the Action of Sodium Amide in Liquid Ammonia on Butanal

The synthesis of propyl-2-aminobutyl ether was attempted, as indicated by the equations below, in an effort to produce a desired intermediate:



The first of these reactions proceeded as indicated; however, the reaction product of (1), an aldehyde ammonia, was in equilibrium with water and the corresponding imine, as indicated by the equation:



The water from this equilibrium was removed by sodium amide, forcing the reaction to the right and producing the imine. Imines condense in the presence of sodium amide or on heating[46, 47]. It was found that reactions (2) and (3), above, never proceeded.

Several attempts, some with the addition of butyl bromide and some without it, yielded products which boiled over a range from 60°/atms. to 175°/10 mm. After the residue was cooled black, solid polymers were left in the distillation flask. It appears probable that the products of these reactions were polymerized imines. There were no indications of desired products having been formed. For this reason work on these reactions was discontinued.

Reaction of a Grignard Reagent with Diiodoacetylene-(1,2-di-iodoethyne)

The following reactions were attempted:

$$2I_2 + H{-}C{\equiv}C{-}H \xrightarrow{NH_3} 2HI + I{-}C{\equiv}C{-}I \qquad (1)$$

$$CH_3{-}CH_2{-}CH_2{-}CH_2{-}Br + Mg \xrightarrow{ether}$$

$$CH_3{-}CH_2{-}CH_2{-}MgBr \qquad (2)$$

$$(C_2H_5)_2NH + CH_3{-}CH_2{-}CH_2{-}MgBr \longrightarrow$$

$$(C_2H_5)_2NMgBr + C_4H_{10} \qquad (3)$$

$$I{-}C{\equiv}C{-}I + 2(C_2H_5)_2NMgBr \longrightarrow$$

$$(C_2H_5)_2N{-}C{\equiv}C{-}N(C_2H_5)_2 + 2MgBr \qquad (4)$$

Reactions (1), (2), and (3) gave satisfactory results. The addition of the Grignard reagent to diiodoacetylene (4)

produced a tar. The following procedure was employed:

One hundred grams of iodine were placed in a two-liter, three-necked, round bottomed flask equipped with a reflux condenser and compressed air stirrer. The contents of the flask were cooled in an acetone-dry ice bath. Seven hundred and fifty milliliters of ammonia were added as rapidly as possible. Although a violent reaction took place and a small amount of iodine vapor was lost, the procedure has been reported to be perfectly safe[48]. Acetylene from a cylinder was washed with water, bubbled through concentrated sulfuric acid and then passed through a soda lime tower and bubbled through the iodine solution.

The solution was dark brown but after two and one-half hours it became perfectly clear. The ammonia was evaporated to about 150 ml., and 500 ml. of water were added to precipitate the diiodoacetylene which was a white crystalline solid. The solution was suction filtered, and the diiodoacetylene was dried in a calcium chloride desiccator. Air-drying and drying in a sulfuric acid desiccator caused decomposition. The yield was 54 grams or 99 per cent of the theoretical based upon iodine.

The butyl magnesium bromide was prepared in the usual manner from 9.6 g. of magnesium metal and 53.6 g. of butyl-bromide in 150 ml. of dry ether. A solution of 28.4 g. of diethylamine in 150 ml. of dry ether was added dropwise into

the flask containing the Grignard reagent. Ether was added when needed, and the solution was maintained at refluxing temperature for an hour.

Fifty-five and one-half grams of diiodoacetylene dissolved in 150 ml. of dry ether were added dropwise to the flask containing the diethylamine-Grignard reagent while the mixture was warmed on a water bath. After one hour, the ether was removed on a steam bath. The residue was a black, tar-like mass. This general procedure was varied in several similar attempts, but a tar was obtained in each case.

CHAPTER III

PROCEDURES FOR SYNTHESIS OF UNSATURATED AMINO-ETHERS

Synthesis of β-Dialkylaminoethanols:

$$H_2C\text{--}CH_2\ (O) + HNR_2 \xrightarrow{H_2O\ catalyst} R_2N\text{--}CH_2\text{--}CH_2\text{--}OH$$

The general procedure followed to prepare the dimethyl, di-n-propyl, di-iso-propyl, and di-n-butyl analogs of aminoethanol was:

One and one-half moles of the appropriate amine and about 100 ml. of water were placed in a flask equipped with a stirrer, a reflux condenser, and a gas inlet tube. The tip of the tube reached below the surface of the solution.

Four moles of liquid ethylene oxide were vaporized at room temperature and passed through the inlet tube into the amine solution. Moderate heating and stirring were maintained until an hour after completion of the four-hour addition period.

Two layers were present; the lower layer, most of which was water, was discarded. To the upper layer, 150 ml. of anhydrous dioxane were added, and the mixture was fractionated.

The forerun, containing dioxane and water azeotrope and anhydrous dioxane, was followed by the product. In some

cases the upper layer was dried with sodium hydroxide. Yields, based upon the amine employed, were between 40 and 70 per cent.

The boiling points of the compounds thus prepared are listed in Table I in Chapter V.

Synthesis of Allyl-(2-aminoethyl) Ether:

$$CH_2{=}CH{-}{-}CH_2{-}{-}O{-}{-}CH_2{-}{-}CH_2{-}{-}NH_2$$

In a two-liter, three-necked, round bottomed flask equipped with a stirrer and a reflux condenser, the outlet of which was terminated by a calcium chloride tube, were placed 122 g. (two moles) of commercial mono-ethanolamine and 500 ml. of toluene. The mixture was heated to refluxing temperature, and 46 g. (two moles) of metallic sodium were added in small pieces over a period of four and one-half hours. After the reaction had started, the heat produced was almost sufficient to maintain refluxing. Refluxing temperature was maintained for four hours after completing the addition of sodium. Two hundred and forty-two grams (2 moles) of allyl bromide were then added from a dropping funnel at a rate which maintained refluxing without external heating. After the addition had been completed, heating was resumed and refluxing was maintained for three hours.

The toluene solution of allyl-(2-aminoethyl) ether was extracted three times with 200 ml. portions of 6 M

solution of hydrochloric acid. The extracts were combined and made basic by addition of a large excess of sodium hydroxide solution. The upper layer was separated and dried over anhydrous barium hydroxide overnight. The barium hydroxide was filtered off, and an attempt was made to fractionate the mixture. Since the distillate separated into two layers, it was returned to the original mixture which was then dried over solid sodium hydroxide overnight. After the sodium hydroxide had been filtered off, the mixture was distilled through a 3.5 foot column packed with very small Berl saddles.

The fraction collected from 136-137° weighed 30.5 g., a yield of 14.8 per cent of the theoretical based upon mono-ethanolamine. Twenty or thirty milliliters of a high-boiling material, probably mono-ethanolamine, remained in the pot.

No doubt the loss incurred in the isolation of the product contributed to the low yield.

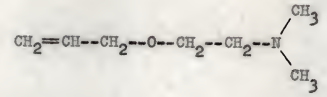
Allyl-(2-aminoethyl) Ether

$$NH_2\text{--}CH_2\text{--}CH_2\text{--}OH + Na \longrightarrow NH_2\text{--}CH_2\text{--}CH_2\text{--}ONa + \tfrac{1}{2}H_2$$

$$NH_2\text{--}CH_2\text{--}CH_2\text{--}ONa + Br\text{--}CH_2\text{--}CH{=}CH_2 \longrightarrow NH_2\text{--}CH_2\text{--}CH_2\text{--}O\text{--}CH_2\text{--}CH{=}CH_2 + NaBr$$

Molecular Formula	$C_5H_{11}NO$
Molecular Weight	101.1
Boiling Point	136-137
Refractive Index ($n^{25}D$)	1.4353
Density (d^{25}_4)	0.8627
Molar Refraction (MR_D) :	
Theoretical	29.98
Found	29.91
Analysis -- Nitrogen, % :	
Calculated	13.85
Found	13.77
Yield of Purified Product, %	14.8

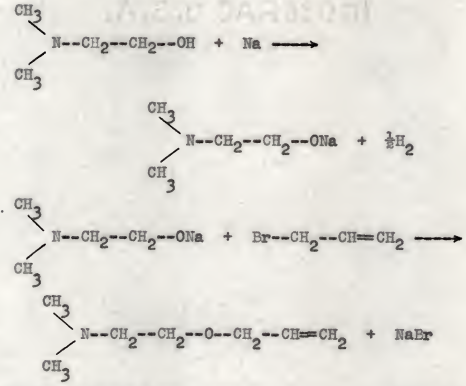
Synthesis of Allyl-(2-dimethylaminoethyl) Ether:



Eighty-nine and one-tenth grams (one mole) of β-dimethylaminoethanol were placed in a one-liter, three-necked flask equipped with a stirrer and a reflux condenser. A thermometer was fitted into the third neck so that the bulb was immersed in the liquid.

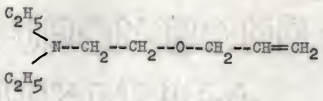
Two hundred milliliters of benzene were added. The solution was stirred, and 23 g. (one mole) of metallic sodium were added in small pieces over a period of four hours. Refluxing temperature was maintained, with external heat being supplied when needed, throughout the addition and for one hour after its completion. The thermometer in the third neck was replaced by a dropping funnel, and 121 g. (one mole) of allyl bromide were added dropwise over a period of one and one-half hours. An additional two hundred milliliters of benzene were added to the mixture and it was then filtered to remove the sodium bromide. This filtrate, after overnight drying with solid sodium hydroxide, was fractionated. The portion boiling from 145-147° was collected. This product weighed 38.5 g., a yield of 33.6 per cent of the theoretical based upon the β-dimethylaminoethanol.

Allyl-(2-dimethylaminoethyl) Ether



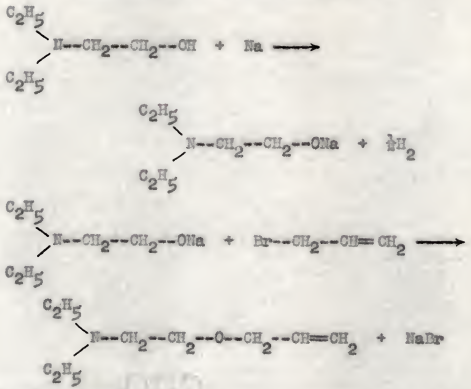
Molecular Formula	$C_7H_{15}NO$
Molecular Weight	129.2
Boiling Point	145-147
Refractive Index ($n^{25}D$)	1.4228
Density (d^{25}_4)	0.8294
Molar Refraction, MR_D :	
Theoretical	39.64
Found	39.64
Analysis -- Nitrogen, % :	
Calculated	10.84
Found	10.79
Yield of Purified Product, %	33.6

Synthesis of Allyl-(2-diethylaminoethyl) Ether:



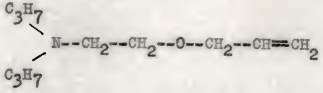
Two hundred milliliters of benzene and 117.1 g. (one mole) of β-diethylaminoethanol were placed in a one-liter, three-necked flask equipped with a stirrer and reflux condenser. A thermometer was fitted into the third neck so that the bulb was immersed in the liquid. The solution was stirred, and 23 g. (one mole) of metallic sodium were added in small pieces over a period of four hours. Refluxing temperature was maintained, with external heat being supplied when necessary, throughout the addition and for one hour after its completion. The thermometer in the third neck was replaced by a dropping funnel, and 121 g. (one mole) of allyl bromide were added dropwise over a period of one and one-half hours. An additional two hundred milliliters of benzene were added to the mixture which was then filtered to remove the solid sodium bromide. Solid sodium hydroxide was used as the drying agent. The dry mixture was filtered and fractionated; the portion boiling from 180-183° was collected. The product weighed 50.5 g., representing a yield of 32.1 per cent of the theoretical based upon β-diethylamino-ethanol.

Allyl-(2-diethylaminoethyl) Ether



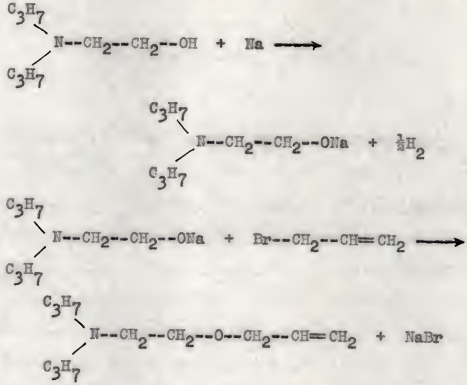
Molecular Formula	$C_9H_{19}NO$
Molecular Weight	157.2
Boiling Point	180-183
Refractive Index (n^{25}_D)	1.4306
Density (d^{25}_4)	0.8330
Molar Refraction (MR_D) :	
Theoretical	48.88
Found	48.86
Analysis -- Nitrogen, % :	
Calculated	8.92
Found	8.84
Yield of Purified Product, %	32.1

Synthesis of Allyl-(2-di-n-propylaminoethyl) Ether:



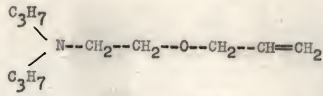
Ninety-one grams (0.627 mole) of β-di-n-propylaminoethanol and 300 ml. of toluene were placed in a one-liter, three-necked flask equipped with a stirrer, reflux condenser and thermometer. An equivalent amount of sodium (0.627 mole) was added and refluxing was maintained for four hours. An equivalent amount of allyl bromide (0.627 mole) was then added dropwise and refluxing maintained for four hours after completion of the addition. The mixture was then filtered to remove the sodium bromide, and the filtrate was extracted twice with 6 M hydrochloric acid solution. The acid extracts were combined and made basic by addition of a large excess of saturated sodium hydroxide solution. The amine layer was separated, dried over anhydrous barium hydroxide, filtered, and fractionated at reduced pressure. A yield of 51 g., or 41 per cent of the theoretical based upon β-di-n-propylaminoethanol, resulted.

Allyl-(2-di-n-propylaminoethyl) Ether



Molecular Formula	$C_{11}H_{23}NO$
Molecular Weight	185.3
Boiling Point	117-118/41 mm.
Refractive Index ($n^{25}D$)	1.4328
Density (d^{25}_4)	0.8289
Molar Refraction (MR_D) :	
Theoretical	58.11
Found	58.08
Analysis -- Nitrogen, % :	
Calculated	7.56
Found	7.52
Yield of Purified Product, %	41.0

Synthesis of Allyl-(2-di-isopropylaminoethyl) Ether:

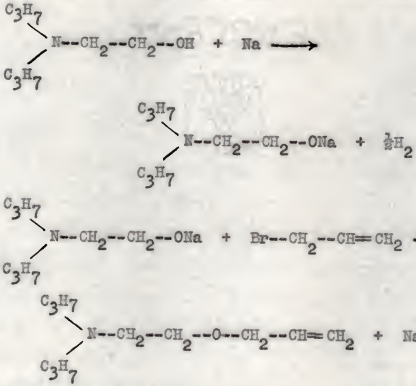


Twelve and one-tenth grams (0.527 mole) of sodium and 400 ml. of toluene were placed in a two-liter, round-bottomed flask equipped with a dropping funnel, stirrer, reflux condenser, and heating mantle. The contents of the flask were heated to refluxing temperature. The heat and stirring created a suspension of small droplets of sodium. To this slurry, 72.6 g. (0.500 mole) of di-isopropylaminoethanol were added dropwise. Stirring and refluxing, maintained during the forty-five minute addition period, were continued for four hours. Sixty-four grams of allylbromide (0.527 mole) were then added dropwise, and stirring and heating were continued for two hours after completion of this addition.

The mixture was filtered to remove the sodium bromide which had formed, and the filtrate was dried over solid sodium hydroxide. Filtration to remove the solid sodium hydroxide, followed by distillation at reduced pressure yielded 62 g. of the product. This represents a 67 per cent yield based upon the 2-isopropylaminoethanol.

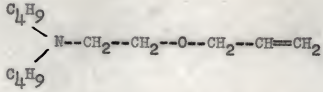
It should be noted that a 5.89 per cent excess of sodium and an equivalent excess of allyl bromide were employed.

Allyl-(2-di-iso-propylaminoethyl) Ether



Molecular Formula	$C_{11}H_{23}NO$
Molecular Weight	185.3
Boiling Point	108-110/40 mm.
Refractive Index ($n^{25}D$)	1.4353
Density (d^{25}_4)	0.8322
Molar Refraction (MR_D) :	
Theoretical	58.13
Found	58.14
Analysis -- Nitrogen, % :	
Calculated	7.56
Found	7.48
Yield of Purified Product, %	67.0

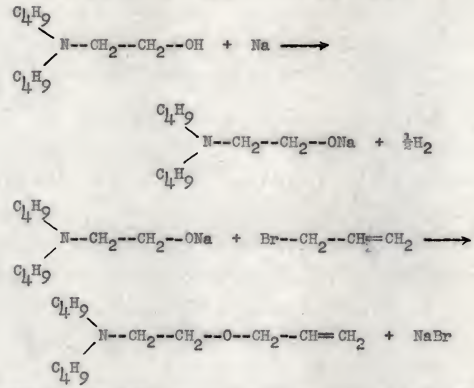
Synthesis of Allyl-(2-di-n-butylaminoethyl) Ether



Sixty-six grams (0.381 mole) of di-n-butylaminoethanol were added dropwise to 8.8 g. (0.381 mole) of molten sodium suspended in toluene in a one-liter, three-necked flask equipped with a dropping funnel, stirrer, reflux condenser, and heating mantle. Stirring and refluxing, maintained during the one-half hour addition period, were continued for four hours after completion of the addition of the di-n-butylaminoethanol. Forty-six and two tenths grams (0.381 mole) of allyl bromide were then added dropwise, and stirring and heating were continued for two hours after completion of this addition.

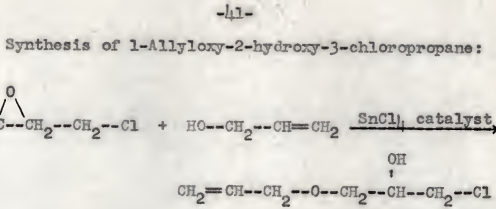
The mixture was filtered, removing the sodium bromide which had formed, and the filtrate was dried over solid sodium hydroxide. Removal of the solid sodium hydroxide was followed by distillation, producing a fraction which boiled at 111.4-111.6/10 mm. The yield of allyl-(2-di-n-butylaminoethyl) ether was 47.3 per cent of the theoretical amount, based upon di-n-butylaminoethanol or sodium.

Allyl-(2-di-n-butylaminoethyl) Ether



Molecular Formula	$C_{13}H_{27}NO$
Molecular Weight	213.3
Boiling Point	111.4-111.6/ 10mm.
Refractive Index ($n^{25}D$)	1.4373
Density (d^{25}_4)	0.8240
Molar Refraction (MR_D) :	
Theoretical	67.40
Found	67.43
Analysis -- Nitrogen, % :	
Calculated	6.58
Found	6.67
Yield of Purified Product, %	47.3

Synthesis of 1-Allyloxy-2-hydroxy-3-chloropropane:



The stannic chloride used as the catalyst in the condensation of epichlorohydrin and allyl alcohol was prepared by passing gaseous chlorine over metallic tin and condensing the stannic chloride.

Two hundred two and three-tenths grams (4 moles) of allyl alcohol and 0.5 g. (0.002 mole) of stannic chloride were placed in a one-liter, three-necked flask equipped with a dropping funnel, stirrer, and reflux condenser. The contents of the flask were cooled to about 15°, and 92.5 g. (one mole) of epichlorohydrin were added dropwise through the funnel while the contents of the flask were stirred. After completion of the addition, the reaction mixture was stirred and maintained at refluxing temperature for three hours.

The reaction mixture was dried with sodium sulfate and distilled through a Vigreux column. A 128 g. fraction was collected between 175 and 185°, representing an 85 per cent yield of 1-allyloxy-2-hydroxy-3-chloropropane based upon epichlorohydrin.

The reaction was attempted using stannic chloride

with water of hydration, but the yield was negligible.

This reaction was also run using sulfuric acid as the catalyst. The procedure followed was:

Five moles of epichlorohydrin and 13 moles of allyl alcohol were mixed and 23.4 g. of concentrated sulfuric acid were added dropwise. The mixture was maintained at refluxing temperature for six hours, cooled, and an excess of barium carbonate (100 g.) was added. Fractionation of the filtrate after the removal of the barium sulfate produced a 32.7 per cent yield based upon epichlorohydrin.

Synthesis of 1-Allyloxy-2-hydroxy-3-aminopropane:

$$CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}\overset{OH}{\overset{|}{C}}H{-}CH_2{-}NH_2$$

Fifteen and two-tenths grams (0.66 mole) of sodium were converted to sodium amide in 800 ml. of liquid ammonia contained in a one-liter, round-bottomed flask fitted with a stirrer, a dropping funnel, and a gas exit tube. A small, dry crystal of ferric nitrate was used as the catalyst in accordance with the method of Vaughn, Vogt, and Nieuwland[49].

To the sodamide suspended in liquid ammonia, 92 g. (0.609 mole) of 1-allyloxy-2-hydroxy-3-chloropropane were added dropwise over a one-hour period. Liquid ammonia was added to the flask to compensate for loss due to evaporation during the addition period. Then no more was added, but stirring was continued until the volume of solution remaining in the flask had diminished, due to the evaporation of ammonia, to about 200 ml. One hundred milliliters of water followed by 200 ml. of ether were cautiously added through the dropping funnel.

The layers were separated and the water layer was extracted twice with 50 ml. portions of ether. The ether solutions were combined, dried with sodium sulfate, and fractionated. The fraction boiling at 152-154° and weighing

30.0 g. was collected, representing a yield of 37.5 per cent based upon 1-allyloxy-2-hydroxy-3-chloropropane.

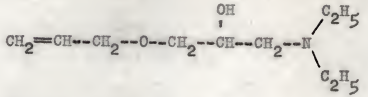
1-Allyloxy-2-hydroxy-3-aminopropane

$$CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}\overset{OH}{\overset{|}{C}}H{-}CH_2{-}Cl + NaNH_2 \xrightarrow[\text{solvent}]{NH_3}$$

$$CH_2{=}CH{-}CH_2{-}O{-}CH_2{-}\overset{OH}{\overset{|}{C}}H{-}CH_2{-}NH_2 + NaCl$$

Molecular Formula	$C_6H_{13}NO_2$
Molecular Weight	131.2
Boiling Point	152-154
Refractive Index ($n^{25}D$)	1.4340
Density ($n^{25}4$)	0.9614
Molar Refraction (MR_D) :	
Theoretical	36.13
Found	35.53
Analysis -- Nitrogen, % :	
Calculated	10.69
Found	10.77
Yield of Purified Product, %	37.5

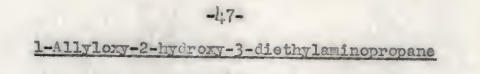
Synthesis of 1-Allyloxy-2-hydroxy-3-diethylaminopropane:



A mixture of 70.5 g. (0.467 mole) of 1-allyloxy-2-hydroxy-3-chloropropane and 85.0 g. (2.5 moles) of diethylamine were placed in a round-bottomed, two-necked flask equipped with a reflux condenser and stirrer. Stirring and refluxing temperature were maintained during eight hours. The cooled reaction mixture was made basic by the addition of sodium hydroxide solution. The amine layer was separated, and the residue was extracted with 100 ml. of ether. The combined amine layer and ether extract were dried over solid sodium hydroxide. After the ether had been removed on a steam bath, the residue was fractionated at reduced pressure. Twenty-eight grams of 1-allyloxy-2-hydroxy-3-diethylaminopropane were obtained, representing a yield of 32 per cent based upon 1-allyloxy-2-hydroxy-3-chloropropane.

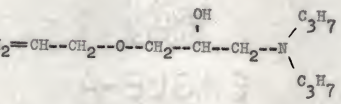
This yield could undoubtedly be improved by maintaining the reaction conditions for a longer period of time.

1-Allyloxy-2-hydroxy-3-diethylaminopropane



Molecular Formula	$C_{10}H_{21}NO_2$
Molecular Weight	187.3
Boiling Point	87.5-88.5/3 mm.
Refractive Index ($n^{25}D$)	1.4470
Density (d^{25}_4).....	0.9118
Molar Refraction (MR_D) :	
Theoretical	55.02
Found	54.88
Analysis -- Nitrogen, % :	
Calculated	7.49
Found	7.57
Yield of Purified Product, %	32.0

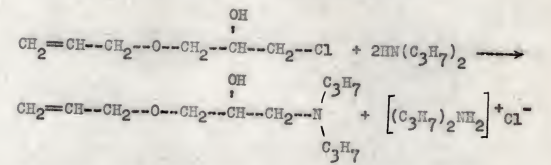
Synthesis of 1-Allyloxy-2-hydroxy-3-di-n-propylamino-propane:



Sixty-two grams (0.411 mole) of 1-allyloxy-2-hydroxy-3-chloropropane and 166 g. (1.64 moles) of di-n-propylamine in a three-necked, round-bottomed flask fitted with a stirrer, reflux condenser and thermometer were stirred and heated to 100° during forty-eight hours. The di-n-propylamine hydrochloride was removed. The filtrate was dried with sodium sulfate and fractionated at 2 mm. pressure.

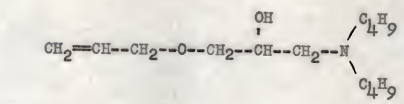
Fractionation gave 63 g. of product, representing a yield of 71 per cent of the theoretical based upon 1-allyloxy-2-hydroxy-3-chloropropane.

1-Allyloxy-2-hydroxy-3-di-n-propylaminopropane



Molecular Formula	$C_{12}H_{25}NO_2$
Molecular Weight	215.3
Boiling Point	109.5-111.5/2 mm.
Refractive Index ($n^{25}D$)	1.4472
Density ($d^{25}4$)	0.9045
Molar Refraction (MR_D) :	
Theoretical	64.33
Found	63.90
Analysis -- Nitrogen, % :	
Calculated	6.50
Found	6.54
Yield of Purified Product, %	71

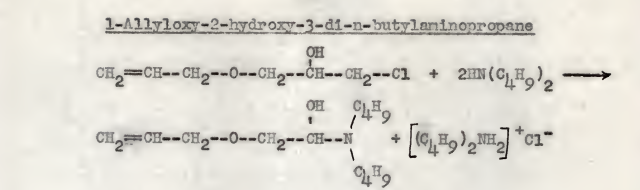
Synthesis of 1-Allyloxy-2-hydroxy-3-di-n-butylaminopropane:



A mixture of 75.3 g. (0.50 mole) of 1-allyloxy-2-hydroxy-3-chloropropane and 258.5 g. (2.00 moles) of di-n-butylamine, in a one-liter flask fitted with a reflux condenser was heated on a steam-bath for twenty hours. The precipitate of di-n-butylamine hydrochloride was removed, dried in a sulfuric acid desiccator, and weighed. Thirty grams of amine salt were obtained. Heating the filtrate fifteen hours longer gave 18 g. more of the hydrochloride; twenty hours additional heating yielded another 17.5 grams. A total yield of 65.5 g. of the amine hydrochloride was obtained after fifty-five hours heating on a steam-bath, indicating the reaction was probably 79 per cent complete.

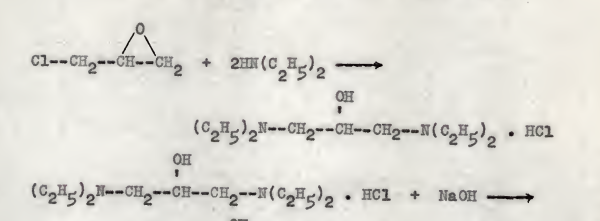
The final filtrate was dried with solid sodium carbonate and fractionated at 2 mm. pressure. Sixty-three grams of product was collected, representing a yield of 52 per cent based upon 1-allyloxy-2-hydroxy-3-chloropropane.

1-Allyloxy-2-hydroxy-3-di-n-butylaminopropane



Molecular Formula	$C_{14}H_{29}NO_2$
Molecular Weight	243.4
Boiling Point	120-122/2 mm.
Refractive Index ($n^{25}D$)	1.4488
Density (d^{25}_4)	0.8920
Molar Refraction (MR_D) :	
Theoretical	73.6
Found	72.2
Analysis -- Nitrogen, % :	
Calculated	5.77
Found	5.82
Yield of Purified Product, %	52

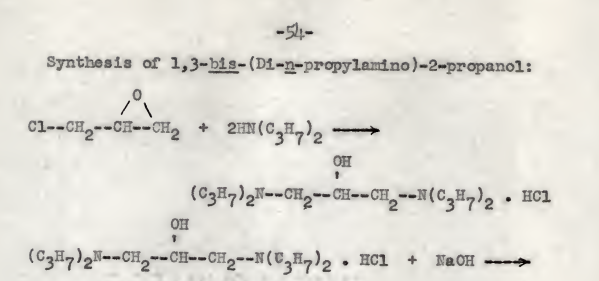
Synthesis of 1,3-bis-(Diethylamino)-2-propanol:



A mixture of 107.4 g. (1.16 moles) of epichlorohydrin (1,2-epoxy-3-chloropropane) and 241.0 g. (2.92 moles) of diethylamine was placed in a two-necked, round-bottomed flask equipped with a reflux condenser, stirrer, and heating mantle. The mixture was kept under reflux and was stirred until a brisk reaction had set in (about two hours). Stirring was continued until the reaction had subsided. Three hundred milliliters of water and 200 ml. of concentrated hydrochloric acid were added, with cooling, to the semi-solid mass. The solution was extracted twice with ether, made alkaline, and again extracted. The latter extract was dried with solid sodium hydroxide, the ether was removed on a steam bath, and the residue was fractionated at 10 mm. pressure. There was only a very small forerun and only a small amount of

tar-like residue. The product boiled from 105-106°/10 mm. One hundred and fifty-six grams were collected, representing a yield of 66.5% based upon the amount of epichlorohydrin used.

Synthesis of 1,3-bis-(Di-n-propylamino)-2-propanol:

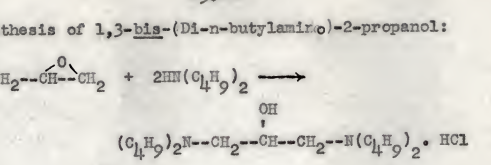


Two hundred and two grams (2 moles) of di-n-propylamine were placed in a one-liter, three-necked, round-bottomed flask fitted with a stirrer, reflux condenser, and dropping funnel. Stirring was begun and 92.5 g. (one mole) of epichlorohydrin was introduced dropwise. The dropping funnel was replaced with a stopper bearing a thermometer. The temperature of the solution was maintained between 100 and 120° during three and one-half hours; external heat was applied when necessary. The amine was freed from its salt with 50 per cent sodium hydroxide, the layers were separated, and the water layer was extracted with 200 ml. of ether. The amine and the ether extract were mixed, dried over solid potassium hydroxide, and distilled off fresh potassium hydroxide. The product boiled at 99-101°/3 mm. One hundred forty-four and one-half grams were obtained, representing a yield

of 56 per cent based upon either epichlorohydrin or di-n-propylamine.

This compound was first prepared by G. B. Bachman and R. L. Mayew[53].

Synthesis of 1,3-bis-(Di-n-butylamino)-2-propanol:



Two hundred eight and six-tenths grams (2 moles) of di-n-butylamine were placed in a one-liter, three-necked flask equipped with an efficient stirrer, reflux condenser, and dropping funnel. Stirring was started and 92.5 g. (one mole) of epichlorohydrin were added dropwise. The dropping funnel was replaced with a stopper bearing a thermometer. The temperature of the solution was maintained between 100 and 120° during three and one-half hours; external heat was used when necessary. Two hundred milliliters of 50 per cent sodium hydroxide were added, the layers were separated, and the aqueous layer was extracted three times, first with two seventy-five milliliter portions and then with one fifty milliliter portion of ether. The combined ether extracts and amine solution were dried over solid potassium hydroxide. Fractionation at reduced pressure gave 180 g. of product representing a yield of 60.2 per cent based upon either

di-n-butylamine or epichlorohydrin. The boiling point of the compound is 163-165°/10 mm.

This compound, which was prepared by Bachman and Mayow in 1945[53], was employed as an intermediate.

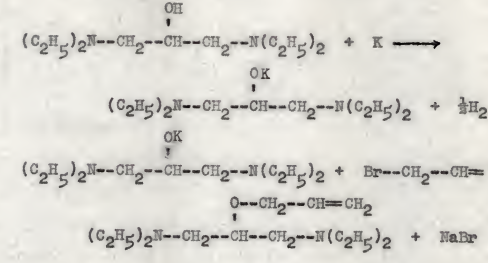
Synthesis of 1,3-bis-(Diethylamino)-2-allyloxypropane:

$$(C_2H_5)_2N\text{--}CH_2\text{--}CH(O\text{--}CH_2\text{--}CH{=}CH_2)\text{--}CH_2\text{--}N(C_2H_5)_2$$

A one-liter, three-necked flask equipped with a mercury-sealed stirrer and a reflux condenser fitted with a calcium chloride tube was charged with 155 g. (0.767 mole) of 1,3-bis-(diethylamino)-2-propanol and 28 g. (0.717 mole) of potassium metal. The third neck of the flask was stoppered and stirring was commenced. After three and one-half hours the mixture had become very thick, and stirring was difficult. Apparently all of the potassium had reacted.

The stopper in the third neck of the flask was replaced by a dropping funnel through which 88 g. (0.727 mole) of allylbromide were introduced. Stirring was continued for forty-five minutes beyond the one-hour addition period. Two hundred milliliters of ether followed by one hundred and fifty milliliters of water were added. The layers were separated; and the ether layer, which was dried over solid potassium hydroxide overnight, was fractionated at reduced pressure through an efficient column to give 75 g. of product, representing a yield of 43.3 per cent based upon the amount of potassium used.

1,3-bis-(Diethylamino)-2-allyloxypropane



Molecular Formula	$C_{14}H_{30}N_2O$
Molecular Weight	242.4
Boiling Point	117.5-118.5/10 mm.
Refractive Index ($n^{25}D$)	1.4432
Density ($d^{25}4$)	0.8503
Molar Refraction, (MR_D) :	
Theoretical	75.91
Found	75.60
Analysis -- Nitrogen, % :	
Calculated	5.78
Found	5.74
Yield of Purified Product, %	43.3

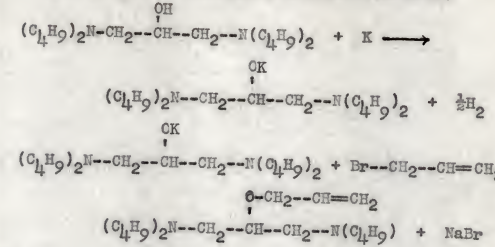
Synthesis of 1,3-bis-(Di-n-butylamino)-2-allyloxypropane:

$$(C_4H_9)_2N{-}CH_2{-}CH(O{-}CH_2{-}CH{=}CH_2){-}CH_2{-}N(C_4H_9)_2$$

One hundred and seventy-seven grams (0.562 mole) of 1,3-bis-(di-n-butylamino)-2-propanol were placed in a one-liter, three-necked, round-bottomed flask equipped with an efficient stirrer and reflux condenser, the outlet of which was fitted with a calcium chloride tube. Seventeen and six-tenths grams (0.450 mole) of potassium metal, which represents 80 per cent of the theoretical amount needed to react with all of the alcohol, were added in small pieces. Meanwhile the third neck of the flask was stoppered. The contents of the flask were heated to about 150° and stirred during eight hours. The stirrer and reflux condenser were removed and replaced with a vacuum distillation take-off head. The excess alcohol was removed at 1.5 mm. After the potassium alcoholate had cooled the stirrer and reflux condenser were replaced, and a dropping funnel was fitted into the third neck. Fifty-four and five-tenths grams (0.45 mole) of allyl bromide were added dropwise with stirring. After one and one-half hours 200 ml. of ether, followed by 300 ml. of water and 100 ml. of saturated sodium hydroxide, were added. The layers were separated. After the ether layer had been dried over solid

sodium hydroxide, it was fractionated at reduced pressure. A yield of 45.5 g., or 28.4 per cent based upon either potassium or allyl bromide, was obtained.

1,3-bis-(Di-n-butylamino)-2-allyloxypropane

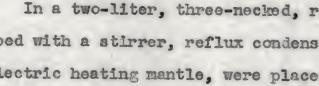


Molecular Formula	$C_{22}H_{46}N_2O$
Molecular Weight	354.6
Boiling Point	160-163/2 mm.
Refractive Index ($n^{25}D$).....	1.4449
Density (d^{25}_4)	0.8448
Molar Refraction (MR_D) :	
Theoretical	112.7
Found	111.7
Analysis -- Nitrogen, % :	
Calculated	3.96
Found	4.00
Yield of Purified Product, %	28.4

Attempted Synthesis of 1,3-bis-(Di-n-propylamino)-2-allyloxy propane:

The potassium alkoxide of 1,3-bis-(di-n-propylamino)-2-propanol was prepared in a manner similar to that employed in the synthesis of the diethyl and di-n-butyl analogs. An excess of allyl bromide was added in an attempt to increase the yield, but the quaternary ammonium bromide formed quite rapidly. Isolation of 1,3-bis-(di-n-propylamino)-2-allyloxy propane was not accomplished since an excess of allyl bromide was employed.

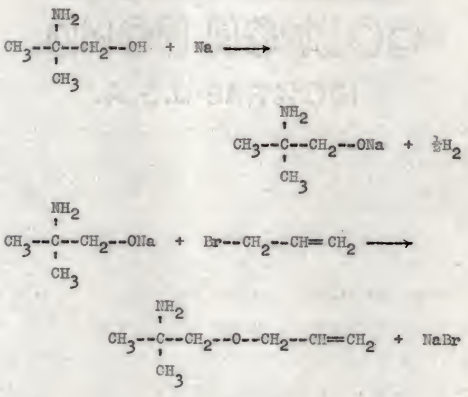
Synthesis of Allyl-(2-amino-2-methylpropyl) Ether:



In a two-liter, three-necked, round-bottomed flask equipped with a stirrer, reflux condenser, dropping funnel, and electric heating mantle, were placed 800 ml. of toluene and 42.1 g. (1.83 moles) of metallic sodium. The toluene was heated to refluxing temperature, melting the sodium, and 162.7 g. (1.83 moles) of 2-amino-2-methyl-1-propanol were added dropwise to the sodium suspension over a period of about one hour. Stirring and heating were then continued for an additional four hours, after which 222.0 g. (1.83 moles) of allyl bromide were added over a period of an hour. These reaction conditions were maintained for three additional hours. The solid sodium bromide was removed, the filtrate was dried with solid sodium hydroxide, and the product was fractionated.

Fractionation at atmospheric pressure produced 158.8 g. of allyl-(2-amino-2-methyl-propyl) ether, representing a yield of 67.5% based upon the 2-amino-2-methyl-1-propanol used.

Allyl-(2-amino-2-methylpropyl) Ether



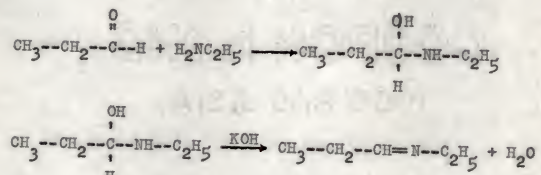
Molecular Formula	$C_7H_{15}NO$
Molecular Weight	129.2
Boiling Point	143.7-144.2
Refractive Index ($n^{25}D$)	1.4251
Density (d^{25}_4)	0.8409
Molar Refraction (MR_D) :	
Theoretical	39.12
Found	39.29
Analysis -- Nitrogen, % :	
Calculated	10.84
Found	10.75
Yield of Purified Product, %	67.5

CHAPTER IV

PROCEDURES FOR REDUCTION OF IMINES WITH LITHIUM ALUMINUM HYDRIDE

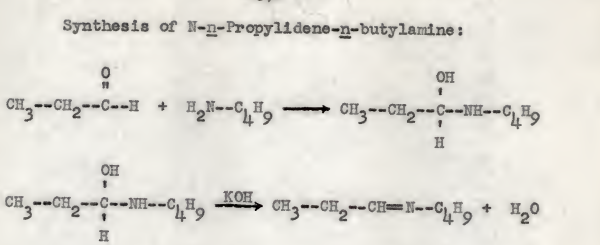
Synthesis of Imines

Synthesis of N-n-Propylidene-ethylamine:



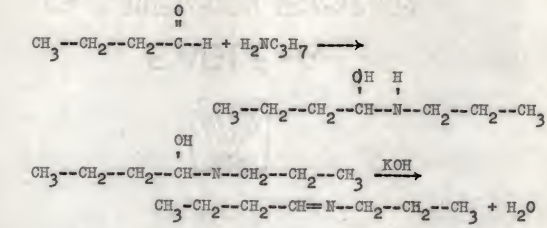
Fourteen and one-half grams (0.25 mole) of n-propionaldehyde were placed in a flask fitted with a stirrer and dropping funnel and cooled to 0°. Sixteen and two-tenths grams of a 70 per cent solution of ethylamine in water (0.25 mole of amine) were added dropwise, and the mixture was cooled. About 5 g. of potassium hydroxide were added, and two layers formed. The upper layer was dried with solid potassium hydroxide and then distilled off fresh potassium hydroxide. The compound boiled between 70 and 75°; the yield of 12.7 g., represented 63 per cent of the theoretical amount based upon either the amine or the aldehyde.

Synthesis of N-n-Propylidene-n-butylamine:



Fourteen and one-half grams (0.25 mole) of n-propionaldehyde were cooled to 0° in a flask fitted with a stirrer and dropping funnel. Then 18.3 g. (0.25 mole) of n-butylamine were added dropwise; stirring and cooling were maintained during the addition. Five grams of potassium hydroxide were added and the mixture was stirred an additional five minutes. Two layers formed, and after seven hours they were separated. The upper layer was dried with solid potassium hydroxide and distilled off fresh potassium hydroxide. A fraction boiling from 120-127° and weighing 20.2 g. was collected. This represents 71 per cent of the theoretical amount based upon either the aldehyde or the amine.

Synthesis of N-n-Butylidene-n-propylamine:



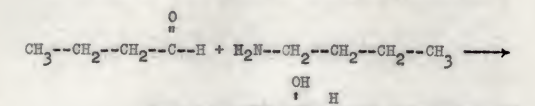
To 18 g. (0.25 mole) of n-butyraldehyde in a flask equipped with a stirrer and dropping funnel and cooled in an ice bath were added dropwise 14.8 g. (0.25 mole) of n-propylamine. The temperature was kept below 2°. After the addition was completed 5 g. of potassium hydroxide were added. Ten hours later the two layers were separated. The upper layer was dried over solid potassium hydroxide for six hours.

Distillation off fresh potassium hydroxide through a Vigreux column produced 19.2 g. boiling between 122 and 127°. This represents a 68 per cent yield of the theoretical amount based upon either the aldehyde or the amine.

Synthesis of N-n-butylidene-iso-propylamine:

To 14.8 g. (0.25 mole) of iso-propylamine cooled in an ice-bath, 18.3 g. (0.25 mole) of n-butyraldehyde were added dropwise over a half hour period while the mixture was being stirred. Upon completion of the addition the aldehyde-amine intermediate was broken up by use of 5 g. of potassium hydroxide. Twelve hours later the layers were separated. The lower layer was discarded, and the upper was dried with solid potassium hydroxide. The drying agent was removed, and fresh potassium hydroxide was added. Distillation gave 16.9 g. of product boiling between 100 and 113°. This represents a 60 per cent yield based upon either the aldehyde or the amine.

Synthesis of N-n-Butylidene-n-butylamine:



To 18.0 g. (0.25 mole) of n-butylamine cooled in an ice-bath, 18.3 g. (0.25 mole) of n-butyraldehyde were added dropwise with stirring. The addition required one-half hour. Five grams of potassium hydroxide were added to help break up the intermediate aldehyde-amine. After twelve hours the layers were separated. The upper layer, the imine, was dried for three hours with solid potassium hydroxide.

Distillation through a Vigreux column gave 19.1 g. of product which represents a yield of 60 per cent of the theoretical amount based upon either the amine or the aldehyde.

The product was a clear colorless liquid, b.p. 143-151°, but turned yellow on standing after about one day.

Rate of Change of Refractive Indexes of Aldimines

A study was undertaken to determine how quickly after distillation alkylaldimines decompose or polymerize. Freshly prepared samples of N-n-butylidene-n-butylamine and N-n-butylidene-n-propylamine were prepared and placed in clear white bottles. The bottles were stored at room temperature in the normal light of the laboratory. The refractive indexes were determined after various intervals of time; the data are presented in Table I. This information is presented graphically in Figure 1.

These data cannot be used to determine the rate of polymerization of aldimines, but they do indicate that more than one reaction takes place. Obviously it is desirable to reduce them as soon after distillation in order to obtain the best possible yields of amines.

TABLE I

CHANGE OF REFRACTIVE INDEXES OF ALDIMINES WITH TIME

N-n-butylidene-n-propylamine		N-n-butylidene-n-butylamine	
Hours after distillation	n^{25}_D	Hours after distillation	n^{25}_D
0.05	1.4123	0.05	1.4179
0.33	1.4120	0.5	1.4172
0.75	1.4119	1.17	1.4172
1.55	1.4119	4.00	1.4174
6.00	1.4124	8.50	1.4178
10.00	1.4126	12.83	1.4181
13.33	1.4129	14.00	1.4186
14.75	1.4139	17.50	1.4190
15.75	1.4131	25.60	1.4198
18.03	1.4133	29.00	1.4186
22.70	1.4139	38.00	1.4210
26.50	1.4143	one week	1.4344
29.45	1.4132		
38.55	1.4165		
42.00	1.4170		
one week	1.4308		

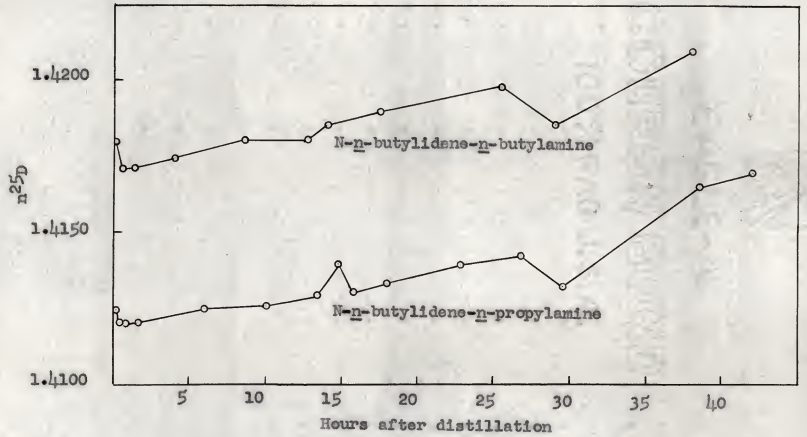


FIGURE 1

REFRACTIVE INDEXES OF ALDIMINES vs TIME AFTER DISTILLATION

Preparation of a Standard Solution of Lithium Aluminum Hydride in Diethyl Ether:

The solubility of lithium aluminum hydride in diethyl ether at 25° is 25-30 g. per 100 g. of solvent[50]. Highly concentrated solutions are quite viscous; more dilute solutions are easier to handle.

Anhydrous diethyl ether was employed since a solvent containing moisture or alcohol will react to coat the hydride with oxides or alcoholates which will diminish the rate at which the hydride dissolves.

A solution was prepared by refluxing a mixture of 79.7 g. of lithium aluminum hydride and three liters of dry ether six hours. The system was protected from moisture and carbon dioxide of the atmosphere by a soda-lime tube at the exit of the reflux condenser.

In spite of careful technique in preparing the solution, a small amount of insoluble material remained. The solution was filtered very rapidly through paper in a Buchner funnel and then placed in a tightly stoppered bottle. The amount of insoluble material was found to be surprisingly small. Although the solution was clear after filtration, within three hours a small amount of insoluble material had formed. This precipitate was undoubtedly due to reactions which took place while the solution was in contact with the

air.

Lithium aluminum hydride hydrolyzes easily and quantitatively:

$$LiAlH_4 + 4H_2O \longrightarrow LiOH + Al(OH)_3 + 4H_2$$

This property has been employed by other investigators for the determination of the concentration of lithium aluminum hydride solutions[51].

A diagram of the apparatus employed for the assay is shown in Fig. 2. The apparatus was constructed so that the hydrolysis could be carried out at constant temperature and volume. The hydrogen gas evolved by decomposition was measured by increase in pressure.

A two-liter round-bottomed flask with a standard taper joint was used. A modified dropping funnel having a pressure-equilizing by-pass and take-off arm leading to a manometer was securely attached to the flask with thermoplastic cement. The funnel was closed with a tightly fitting rubber stopper. The outlets of the dropping funnel were closed with a glass rod. One end of the rod was ground to fit the lower opening and the other end extended through a glass tube fitted through a rubber stopper closing the upper opening. The glass tube was fastened to the rod with rubber tubing. The rod could be raised slightly, due to the flexibility of the rubber tubing, to open the lower outlet of the

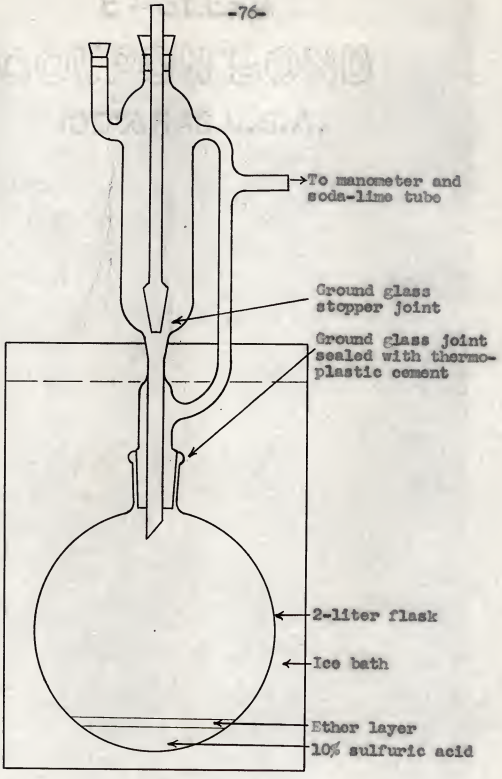


FIGURE 2

STANDARDIZATION APPARATUS

funnel without releasing the pressure of the system.

The decomposition flask was clamped into place and was surrounded by an ice-bath. A mixture of 160 ml. of cold 10 per cent sulfuric acid and 40 ml. of cold ether were added. The upper portion of the apparatus was then fastened in place and sealed with thermo-plastic cement. The apparatus was allowed to stand for several minutes with the pinch clamp closed. If any change of pressure was noticed the clamp was opened momentarily. The process was repeated until equilibrium was reached.

Ten milliliters of lithium aluminum hydride solution were placed in the upper part of the apparatus. The system was closed and was allowed to stand a few minutes to insure equilibrium. The solution was then added slowly into the reaction flask. After equilibrium had been reached the change in pressure was read from the manometer. The system was prepared for subsequent analysis by opening the pinch clamp.

The concentration of hydride was calculated from the equation:

$$\text{Molarity} = \frac{\text{pressure increase (mm. of Hg) x volume (ml.)}}{\text{volume of sample (ml.) x } 68{,}100}$$

The volume is the total volume of the system less the volume of all solutions added. The factor 68,100 combines R, T, and the fact that 4 moles of hydrogen are liberated per

mole of lithium aluminum hydride.

The average of three determinations indicated a molarity of 0.6028. The individual determinations are listed below:

	First	Second	Third
Volume (ml.)	1954	1944	1934
Volume of sample (ml.)	10.00	10.00	10.00
Pressure increase (mm. of Hg)	21.10	21.10	21.15
Molarity	0.6045	0.6023	0.6007

The solution was stored in a tightly closed flask. It was assayed at various times and was found to keep very well.

Although it is more convenient to measure the number of milliliters of solution desired than to weigh solid hydride and prepare a new solution each time a reduction is run, the weighing-procedure was followed in some cases.

Reduction of Alkylaldimines with Lithium Aluminum Hydride

Each of the five imines, prepared as has been described, was reduced with lithium aluminum hydride within one-half hour after its preparation. In each case the imino was added to a fifty per cent excess of the hydride in an ether solution, and the adduct was hydrolyzed with slightly more than the theoretical amount of water. The mixture was filtered and the ether solution dried and fractionated. The corresponding secondary bases were obtained in each case. The amount of by-products formed was negligible.

Attempts to use weakly or strongly basic water solutions for the hydrolysis of the addition products, $(RCH_2NR)_4LiAl$, produced a very gelatinous precipitate which made filtration difficult and lowered the yields. It was found that hydrolysis with about a 20 per cent excess of the theoretical amount of water gave a precipitate that was more granular and therefore easier to remove by filtration. Acids could not be used for hydrolysis because they do not facilitate isolation of amines.

The following procedure is an example of the method employed:

Reduction of N-n-propylidene-ethylamine:

$$4CH_3\text{--}CH_2\text{--}CH_2\text{--}CH{=}N\text{--}C_2H_5 \;+\; LiAlH_4 \longrightarrow$$

$$(CH_3\text{--}CH_2\text{--}CH_2\text{--}CH_2N\text{--}C_2H_5)_4LiAl \xrightarrow{4HOH}$$

$$CH_3\text{--}CH_2\text{--}CH_2\text{--}CH_2\text{--}\overset{H}{N}\text{--}C_2H_5 \;+\; LiOH \;+\; Al(OH)_3$$

A solution of 92.5 ml. of 0.603 M lithium aluminum hydride in ether (0.0558 mole, 50 per cent excess of hydride) and 200 ml. of dry ether were placed in a one-liter three-necked flask equipped with a reflux condenser, dropping funnel, and stirrer, and protected from moisture until completion of the reaction by a soda-lime tube attached to the opening. Through the dropping funnel, 12.7 g. (0.149 mole) of N-n-propylidene-ethylamine were very slowly added. Thirty minutes after completion of the addition 5 ml. of water were added very cautiously. The hydrolysis required about two hours. The mixture was filtered and the precipitate was washed with ether. The filtrate and ether-washings were dried with solid potassium hydroxide.

The product obtained after evaporation of the ether was fractionally distilled. The quantity of fore-run and residue was extremely small. Eight and seven-tenths grams of N-ethyl-n-propylamine were collected from 79.0 to 80.2° (boiling point reported in the literature, 79.8°[52]). This represents a sixty

per cent yield based upon N-n-propylidene-ethylamine. N-ethyl-n-propylamine hydrochloride was prepared in ethyl alcohol and recrystalized from the same solvent. The melting point found was 220-223°, while that recorded in the literature is 223-224°.

In Table VIII the data pertaining to these reductions are listed.

Aldimines prepared as shown on previous pages were reduced without first having been purified by distillation. Since imines polymerize on distillation, the overall yields of secondary amines produced from aldehydes and primary amines are increased by reducing the undistilled imines. A 100 per cent excess of hydride was used in each case, and the excess hydride and addition products were hydrolyzed with a 20 per cent excess of water.

The procedure employed for the synthesis of N-allyl-n-butylamine is illustrative of the method.

Synthesis of N-Allyl-n-butylamine:

$$CH_3\text{--}CH_2\text{--}CH_2\text{--}\overset{O}{\overset{\|}{C}}\text{--}H \;+\; H_2N\text{--}CH_2\text{--}CH{=}CH_2 \xrightarrow{KOH}$$

$$CH_3\text{--}CH_2\text{--}CH_2\text{--}CH{=}N\text{--}CH_2\text{--}CH{=}CH_2 \;+\; H_2O$$

$$4CH_3\text{--}CH_2\text{--}CH_2\text{--}CH{=}N\text{--}CH_2\text{--}CH{=}CH_2 \;+\; LiAlH_4 \longrightarrow$$

$$(CH_3\text{--}CH_2\text{--}CH_2\text{--}CH_2\text{--}N\text{--}CH_2\text{--}CH{=}CH_2)_4LiAl \xrightarrow{H_2O}$$

$$CH_3\text{--}CH_2\text{--}CH_2\text{--}CH_2\text{--}NH\text{--}CH_2\text{--}CH{=}CH_2 \;+\; LiOH \;+\; Al(OH)_3$$

Eighteen grams (0.25 mole) of n-butyraldehyde in a flask equipped with a stirrer and dropping funnel were cooled in an ice-bath. To the aldehyde 14.3 g. of allylamine were added dropwise while the mixture was stirred. The temperature was kept below 2°. After the addition period 5 g. of potassium hydroxide were added. Ten hours later the two layers were separated. The upper layer was dried over solid potassium hydroxide while stored in the dark at 10° for four hours.

A solution of 4.74 g. (0.125 mole, a 100 per cent excess of lithium aluminum hydride in 300 ml. of dry ether was placed in a one-liter three-necked flask equipped with a reflux condenser, dropping funnel, and stirrer and was protected from moisture until completion of the reaction by a soda-lime tube attached to the opening. Through the dropping funnel, the dried but undistilled N-n-butylidene-allylamine was very slowly added. One hour after completion of the addition

11 ml. of water were added very cautiously. The hydrolysis required about three hours. The mixture was filtered and the filtrate was washed with ether. The filtrate and ether washings were dried with solid potassium hydroxide.

The product obtained after evaporation of the ether was fractionally distilled. Seventeen and one-half grams of N-allyl-n-butylamine or 61.4 per cent based on either the amine or aldehyde were collected between 134 and 135°.

CHAPTER V

CONCLUSIONS AND DISCUSSION OF EXPERIMENTAL RESULTS

Synthesis of Unsaturated Amino-ethers

Several reactions were attempted in an effort to prepare compounds of the general formula:

$$R\text{--}O\text{--}CH_2\text{--}NR_2$$

R may represent alkyl groups or a hydrogen atom.

It is concluded that compounds which have an amino-nitrogen atom and an alkoxy group attached to the same carbon atom hydrolyze very rapidly. Some of the reactions attempted probably produced the aminoethyl ethers; however, if so the yields were extremely low. Both general instability and ready hydrolysis of the compounds contribute to this result.

Ethylene oxide was reacted with secondary amines to produce β-dialkylaminoethanols which were used as intermediates. The boiling points and yields of these compounds are listed in Table II.

The β-dialkylaminoethanols were converted to the respective sodium alkoxides which in turn were reacted with allyl bromide to produce allyl-(2-dialkylaminoethyl) ethers. These compounds are listed with their physical constants and analytical data in Table III.

TABLE II

BOILING POINTS AND YIELDS OF β-DIALKYLAMINOETHANOLS PREPARED FROM AMINES AND ETHYLENE OXIDE

Compound	B.p.°	Yield, %
β-Dimethylaminoethanol	134-135	40.0
β-Di-n-propylaminoethanol	194-198	61.5
β-Di-iso-propylaminoethanol	190-191	70.0
β-Di-n-butylaminoethanol	212-215	65.0

TABLE III

SUMMARY OF PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR ALLYL-(2-DIALKYLAMINOETHYL) ETHERS

Compound	B.p.°	n^{25}_D	d^{25}_4	MR_D		N, %	
				Theor.	Found	Theor.	Found
Allyl-(2-aminoethyl) ether	136-137	1.4353	0.8627	29.98	29.91	13.85	13.77
Allyl-(2-dimethylaminoethyl) ether	145-147	1.4228	0.8294	39.64	39.64	10.84	10.79
Allyl-(2-diethylaminoethyl) ether	180-183	1.4306	0.8330	48.88	48.88	8.92	8.84
Allyl-(2-di-n-propylaminoethyl ether	117-118/41 mm.	1.4328	0.8289	58.11	58.08	7.56	7.52
Allyl-(2-di-iso-propylaminoethyl) ether	108-110/40 mm.	1.4353	0.8322	58.13	58.14	7.56	7.48
Allyl-(2-di-n-butylaminoethyl) ether	111.4-111.6/10 mm.	1.4373	0.8240	67.40	67.43	6.58	6.67

1-Allyloxy-2-hydroxy-3-chloropropane was prepared by reacting epichlorohydrin with allyl alcohol. Fuming stannic chloride was found to be the most efficient catalyst for this reaction. 1-Allyloxy-2-hydroxy-3-chloropropane was reacted directly with secondary amines without having been converted to the epoxide. The products of this reaction, 1-allyloxy-2-hydroxy-3-dialkylaminopropanes, are listed with their physical constants and analytical data in Table IV.

A series of 1,3-bis-(dialkylamino)-2-propanols were prepared by reacting epichlorhydrin with an excess of different secondary amines. These compounds were used as intermediates. They are listed with their boiling points and per cent yields in Table V.

Two 1,3-bis-(dialkylamino)-2-propanols and 2-amino-2-methyl-1-propanol were converted to their respective alkali metal alkoxides which were then reacted with allyl bromide to produce ethers. These compounds are listed in Table VI.

TABLE IV

SUMMARY OF PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR 1-ALLYLOXY-2-HYDROXY-3-DIALKYL-AMINO PROPANES

Compound	B.p.°	$n^{25}D$	$d^{25}4$	MR_D		N, %	
				Theor.	Found	Theor.	Found
1-Allyloxy-2-hydroxy-3-aminopropane	152-154	1.4340	0.9614	36.13	35.53	10.69	10.77
1-Allyloxy-2-hydroxy-3-diethyl-amino-propane	87.5-88.5/3 mm.	1.4470	0.9118	55.02	54.88	7.49	7.57
1-Allyloxy-2-hydroxy-3-di-n-propylamino-propane	109.5-111.5/2 mm.	1.4472	0.9045	64.33	63.90	6.50	6.54
1-Allyloxy-2-hydroxy-3-di-n-butylamino-propane	120-122/2mm.	1.4488	0.8920	73.6	72.2	5.77	5.82

TABLE V

BOILING POINTS AND YIELDS OF 1,3-BIS-(DIALKYL-AMINO)-2-PROPANOLS PREPARED FROM AMINES AND EPICHLOROHYDRIN

Compound	B.p.°	Yield, %
1,3-bis-(Diethylamino)-2-propanol	105-106/ 10 mm.	66.5
1,3-bis-(Di-n-propylamino)-2-propanol	99-101/3 mm.	56
1,3-bis-(Di-n-butylamino)-2-propanol	164-165/10 mm.	60.2

TABLE VI

SUMMARY OF PHYSICAL CONSTANTS AND ANALYTICAL DATA FOR 1,3-BIS-(DIALKYLAMINO-2-ALLYLOXYPROPANE AND ALLYL-(2-AMINO-2-METHYLPROPYL) ETHER

Compound	B.p.°	n^{25}_D	d^{25}_4	MR_D		N, %	
				Theor.	Found	Theor.	Found
1,3-bis-(Diethylamino)-2-allyloxypropane	117.5-118.5/10 mm.	1.4432	0.8503	75.91	75.60	5.78	5.74
1,3-bis-(Di-n-butylamino)-2-allyloxypropane	160-163/2 mm.	1.4449	0.8448	112.7	111.7	3.96	4.00
Allyl-(2-amino-2-methylpropyl) ether	143.7-144.2	1.4251	0.8409	39.12	39.29	10.84	10.75

Recommended Procedure for Synthesis of Amino-ethers

For a large molecular weight alcohol potassium rather than sodium is recommended for the preparation of the alkali metal alkoxide. The alkoxide is best prepared by adding the alcohol dropwise to a suspension of the molten metal in refluxing toluene while the mixture is stirred. The larger the molecular weight of the alcohol the longer is the time necessary for completion of the reaction. Fifty or sixty hours may not be too long a time for very large molecular weight alcohols.

An amount of alkyl halide equivalent to the quantity of alkali metal used is added dropwise and stirring and refluxing temperatures maintained until completion of this reaction. Filtration to remove the alkali metal halide followed by drying and fractionation of the filtrate will yield the product.

A quantity of alkyl halide in excess of the theoretical amount necessary to react with all of the alkali metal should not be used as it will react with the amino-group.

Using the alkali metal in about a five per cent excess of that demanded by theory to react with all of the amino-alcohol will increase the yield.

Reduction of Imines with Lithium Aluminum Hydride

Alkylaldimines were prepared from aldehydes and amines. They are listed with their boiling points and per cent yield in Table VII.

A study of the rates of change of refractive indexes of freshly prepared aldimines showed that the aldimines should be reduced as soon as possible after preparation.

In some cases, a measured amount of standardized solution of lithium aluminum hydride in dry ether was added slowly to an ether solution of the aldimine. In other cases, the hydride was weighed quickly in air and added in powdered form to dry ether in the reaction flask. To this solution the aldimine was added dropwise. In some cases the aldimines were not distilled prior to the addition. This increased the overall yields of secondary amines as based on either the aldehyde or primary amine used to produce the aldimine. The addition products, $(RCH_2NR)_2LiAl$, were hydrolyzed to secondary amines and lithium and aluminum hydroxides with weakly or strongly basic water solutions or with water alone. Acids could not be used for they do not facilitate the isolation of amines from water solutions.

The data resulting from these reductions are listed in Table VII.

TABLE VII

BOILING POINTS AND YIELDS OF ALDIMINES

PREPARED FROM AMINES AND ALDEHYDES

Compound	B.p.°	Yield, %
N-n-Propylidene-ethylamine	71- 75	63
N-n-Propylidene-n-butylamine	120-127	71
N-n-Butylidene-n-propylamine	122-127	68
N-n-Butylidene-iso-propylamine	100-113	60
N-n-Butylidene-n-butylamine	143-151	60

TABLE VIII

DATA ON THE PRODUCTS OF THE REDUCTION OF IMINES

Imine Reduced	Amine Produced	Yield, %	B.P.° of Amine		Characterization Derivatives		
			Found	Recorded	Derivative Used	M.P.° Found	M.P.° Recorded
N-n-Propylidene-ethylamine[a]	N-Ethyl-n-propylamine	60[c]	79-80	79.8	Hydrochloride	220-223	223-224
N-n-Propylidene-n-butylamine[a]	N-n-Propyl-n-butylamine	80[c]	137-139	138-139	Hydrochloride	136.2-137.5	136-137
N-n-Butylidene-n-propylamine[a]	N-n-propyl-n-butylamine	77[c]	137.8-138.5	138-139	Hydrochloride	135-136.5	136-137
N-n-Butylidene-iso-propylamine[a]	N-n-Butyl-iso-propylamine	75[c]	123-125	124-125	Hydrochloride	90-91	91.5-92.5
N-n-Butylidene-n-butylamine[a]	di-n-Butylamine	67[c]	158-160	159	Phenylthiourea	85.2-86	86
N-n-Butylidene-allylamine[b]	N-Allyl-n-butylamine	61.4[d]	134-135	134.2-134.4			
N-n-Butylidene-n-butylamine[b]	di-n-Butylamine	60.2[d]	160-161	159	Phenylthiourea	85-86.1	86
N-n-Propylidene-n-propylamine[b]	di-n-Propylamine	58[d]	109-110.5	110-111	Phenylthiourea	67-69	69

a Purified by distillation; b Dried but not distilled; c Based upon the imine which was reduced; d Based upon the aldehyde used to prepare the imine since the imine was not purified.

This is a new method of preparing secondary alkylamines. Although the method is costly, the procedure is relatively simple, it doesn't require high-pressure equipment or expensive catalysts, the amount of by-products formed is negligible, and the yields are good.

Precautions in Handling Lithium Aluminum Hydride

Although lithium aluminum hydride is a very versatile and useful reagent, it can be quite dangerous unless certain precautions are followed when it or its solutions are handled.

It will burst into flame if left exposed to air for any appreciable length of time. If a few drops of an ether-solution are spilled a fire may be started. When hydrolyzing ether solutions of hydride, hydrogen is released. Consequently, spark-proof stirrer motors are recommended. Lithium aluminum hydride should be stored in tightly sealed containers -- preferably metal containers sealed with paraffin.

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A debt to previous investigators has been incurred in performing this research:

> A new, truly fundamental method of organic chemistry is discovered, at most, every ten years. In practice, however, real success often follows decisively significant, although small, variations in a procedure.[a]

It is hoped that the work presented here, although small, may be of some benefit and significance to organic chemistry.

---

[a] T. Reichstein, Synthetic Methods of Organic Chemistry, by W. Theilheimer, Vol. I, page v, Interscience Publishers, Inc., New York, N. Y.

BIOGRAPHICAL ITEMS

James Luther Smith was born in Terre Haute, Indiana, on January 18, 1924. He pursued his undergraduate studies at the University of Florida and was awarded the degree of Bachelor of Science in Chemistry in June, 1947.

Mr. Smith entered the Graduate School of the University of Florida in August, 1947. While pursuing his Graduate study he held the position of Graduate Assistant from September, 1947, to January, 1948, and from December 1951, to the present time. He held a fellowship provided by a grant from the Office of Naval Research during the period June, 1948, until December, 1950.

Mr. Smith is a member of Gamma Sigma Epsilon and the American Chemical Society.

COMMITTEE REPORT

This dissertation was prepared under the direction of the Chairman of the candidate's Supervisory Committee and has been approved by all members of the Committee. It was submitted to the Graduate Council and was approved as partial fulfilment of the requirements for the degree of Doctor of Philosophy.

Date August 18, 1951

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